Meta-analysis of Randomized Controlled Clinical Studies on Effect of Salmon Calcitonin on Bone Pain in Osteoporosis Patients

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Abstract [**Objectives**] To systematically evaluate the efficacy and safety of salmon calcitonin in the treatment of osteoporosis, and to provide reference for clinical salmon calcitonin treatment and improvement of bone pain symptoms of osteoporosis. [**Methods**] Randomized controlled trials (RCTs) of salmon calcitonin in the treatment of osteoporosis from January 2000 to March 2015 were collected by searching Chinese Biomechanics Literature Database (SinoMed, CBM), China National Knowledge Infrastructure (CNKI), VIP and Wanfang Database. The relevant data of bone pain degree and bone mineral density were extracted to evaluate the methodological quality. Meta-analysis was performed using RevMan 5.1 software. A total of 13 randomized controlled trials involving 1 683 patients were included, including 862 patients in the observation group and 821 patients in the control group. [**Results**] Meta-analysis showed that salmon calcitonin combined with calcium was better than the control group in improving bone pain symptoms in osteoporosis patients, and the difference was statistically significant [*RR* = 1.84, 95% *CI* (1.56, 2.18)]. [**Conclusions**] The salmon calcitonin can significantly improve the bone pain symptoms of the osteoporosis patients, and has no serious adverse reaction. However, due to the small number of studies included in this systematic review and the small sample size, it still needs to be confirmed by high-quality, large sample, multi-center randomized controlled trials.

Key words Salmon calcitonin, Osteoporosis, Bone pain, Meta-analysis

1 Introduction

With the coming of population aging, osteoporosis (OP) has become a common and frequently-occurring disease in the elderly. More and more attention has been paid to the prevention and treatment of osteoporosis. OP is harmful. It can not only cause pain and changes in bone mineral density (BMD), but also affect the quality of life of patients, and bring a heavy burden to society and families[1]. According to statistics, there are currently more than 80 million OP patients in China, and it may increase to 220 million by 2050. At that time, 50% of osteoporotic fractures in the world will occur in Asia, and China accounts for the majority[2].

Salmon calcitonin, as a biological agent, is composed of 32 amino acid single chains and has high biological activity. It can effectively inhibit osteoclast activity, prevent the loss of bone mineral content, alleviate bone pain to a certain extent and maintain high bone mineral density. Therefore, it is widely used in the prevention and treatment of osteoporosis. There is no systematic review of the efficacy of salmon calcitonin in the treatment of osteoporosis. In order to comprehensively understand the efficacy and possible adverse reactions of salmon calcitonin in the prevention and treatment of osteoporosis, it is necessary to systematically evaluate the existing clinical studies.

2 Data and methods

2.1 Retrieval strategy Chinese Biomechanics Literature Database (SinoMed, CBM), China National Knowledge Infrastructure (CNKI), VIP and Wanfang Database were retrieved by computer from January 2000 to March 2022. The references of all the included literatures were manually searched, and the following Chinese journals were manually searched: *Chinese Journal of Orthopaedics*, *Chinese Journal of Osteoporosis*, *China Journal of Orthopaedics and Traumatology*, *Chinese Journal of Traditional Medical Traumatology & Orthopedics*, *The Journal of Cervicodynia and Lumbodynia*, *Chinese Journal of Spine and Spinal Cord*, *and Chinese Journal of Physical Medicine and Rehabilitation*, *etc.* The search terms included: osteoporosis, salmon calcitonin, clinical trial, randomized controlled trial, randomized, and so on.

2.2 Inclusion criteria (i) The type of the original study was a randomized controlled trial (RCTs), quasi-RCTs, and the study was well designed with clear inclusion and exclusion criteria; (ii) the text of the randomized controlled trial must be marked with words describing the random assignment, such as "randomized", "randomly divided into", *etc.*, and can be included in the study regardless of whether the assignment concealment or blinding method is used; (iii) patients with definite diagnosis of OP, regardless of gender, age, course of disease, source of cases, whether the female is menopausal, and the type and dosage of corticosteroids; (iv) interventions, generally salmon calcitonin alone or in combination with calcium in the test group and calcium alone in the control group; (v) the main outcome indicator was the curative effect of bone pain, and the secondary indicators were bone mineral density, quality of life, serum biochemical indicators, adverse reactions and so on.

2.3 Exclusion criteria (i) Literature with incomplete data that cannot be used; (ii) other treatments in addition to salmon calcitonin alone or in combination with calcium; (iii) a series of studies on the same cases only counts their final reported results; (iv) duplicate publications.

2.4 Intervention measures After the completion of the literature search, two independent reviewers carefully read each included RCT literature according to the search strategy, screened and evaluated the quality of the literature according to the pre-set in-

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clusion and exclusion criteria, extracted and cross-checked the data, and discussed and solved the problem together or coordinated by the third researcher if there was any disagreement. All the included literatures were consistent. The main extracted data included: general data: title, author, publication time and source; study characteristics: general information of the subjects, baseline of patients in each group, interventions, randomization method, blindness, loss to follow-up or withdrawal.

2.5 Literature quality and bias evaluation According to the quality evaluation method and bias risk assessment method recommended by Cochrane 5.1.0 evaluation manual, the quality evaluation and bias assessment were carried out for the studies that might meet the inclusion criteria. It mainly includes (i) whether the method of random allocation is correct; (ii) whether the method of allocation concealment is correct; (iii) whether the blind method is used and who is blinded; (iv) whether there is loss to follow-up or withdrawal; if so, whether the intention-to-treat analysis is used; (v) whether the results are selectively reported; (vi) Whether other cases of bias are considered. If the included literatures meet the above quality standards, the possibility of bias is the smallest, it will be judged as grade A; if only one or more items are partially satisfied, the possibility of bias is moderate, it will be judged as B; if the above criteria are not met at all, the likelihood of bias is high, it will be judged as grade C. The risk of bias was plotted using Review Manager 5.1 software.

2.6 Statistical processing Review Manager 5.1 software developed by Cochrane Collaboration Network was used to analyze the statistical heterogeneity of the included studies by x^2 test. If the included studies were not heterogeneous ($P \geqslant 0.10$ or $I^2 \leqslant 50\%$), the fixed effects model was selected for description. On the contrary, when heterogeneity existed ($P < 0.10$ or $I^2 > 50\%$), the causes of heterogeneity, such as course of treatment, dosage, study quality, *etc.*, were found, and subgroup analysis and sensitivity analysis were used to deal with them, and random effects model was used to describe them. In addition, sensitivity analysis and bias analysis were conducted on the results, and descriptive analysis was not suitable for meta-analysis. We also selected the weighted mean difference (WMD). Because the symbol in RevMan version 5.0 and above is "MD", hereinafter referred to as MD), as the effect scale indicator, the 95% confidence interval (*CI*) was calculated, and the difference was statistically significant when $P < 0.05$. Relative risk (*RR*) and 95% *CI* were used for enumeration data, and WMD and 95% *CI* were used for continuous variables.

3 Results and analysis

3.1 General conditions According to the retrieval strategy and screening method, 253 relevant articles were retrieved. After reading the titles and abstracts, 204 articles were excluded because they were repeated, belonged to non-clinical trials or non-randomized concurrent trials, or the purpose of the study was inconsistent with the systematic review, 36 articles were excluded because they did not meet the intervention criteria of the systematic review, and finally 13 RCT articles were included[3-15]. A total of 1 683 patients with chronic osteoporosis were included in the literature, including 862 patients in the treatment group (salmon calcitonin alone or combined with calcium) and 821 patients in the control group (calcium alone).

3.2 Analysis of outcome indicators Eleven articles were included[3,5 13, 15], which reported the improvement of salmon calcitonin combined with calcium on the degree of bone pain in patients with osteoporosis. The results of meta-analysis showed that there was statistical heterogeneity among the studies ($P < 0.1$, $I^2 = 69\%$), and using random effects model with pooled effect size $RR = 1.84$, 95% *CI* [1.56, 2.18], $Z = 7.21$, $P < 0.05$, the difference was statistically significant, suggesting that salmon calcitonin combined with calcium is superior to calcium alone in improving the degree of bone pain in patients with osteoporosis (Fig.1).

Two articles were included[4, 14], which reported the effect of salmon calcitonin on VAS of bone pain in osteoporosis patients. The results of meta-analysis showed that there was statistical heterogeneity among the studies ($P \leqslant 0.1$, $I^2 = 89\%$), and the random effects model was used to analyze, with the pooled effect size $MD = -3.89$, 95% *CI* [−4.89, −3.07], $Z = 8.61$, $P < 0.05$, the difference was statistically significant, suggesting that the VAS score of salmon calcitonin combined with calcium in improving the degree of bone pain in osteoporosis patients was lower than that of single calcium treatment (Fig.2).

3.3 Adverse reactions and treatment Articles[4,6,8,10] reported that salmon calcitonin combined with compound calcium had mild adverse reactions such as flushing, dizziness, nausea, palm flushing, dry mouth and vomiting, which gradually disappeared and were tolerated by most patients. Among them, article[10] reported that one patient withdrew from the study due to intolerable symptoms such as shortness of breath and chest tightness within half an hour after intramuscular injection of salmon calcitonin 50IU. Article[15] reported that one patient withdrew from the study due to nausea and vomiting, and one patient withdrew from the study due to intolerable palpitation.

4 Discussion

Osteoporosis not only causes pain and fracture, but also affects the quality of life of patients, and brings heavy burden to society and families. Therefore, the prevention and treatment of osteoporosis is a very realistic and important issue. At present, many patients with osteoporosis are often only received calcium treatment, or only pay attention to the treatment of osteoporosis complicated with fracture, but neglect the application and prevention of anti-osteoporosis drugs. According to the data of previous studies, the use of calcium alone or calcitonin alone has no significant effect on the improvement of bone pain and bone mineral density in patients with osteoporosis, and may cause complications such as hypocalcemia and secondary hyperthyroidism, which requires the treatment

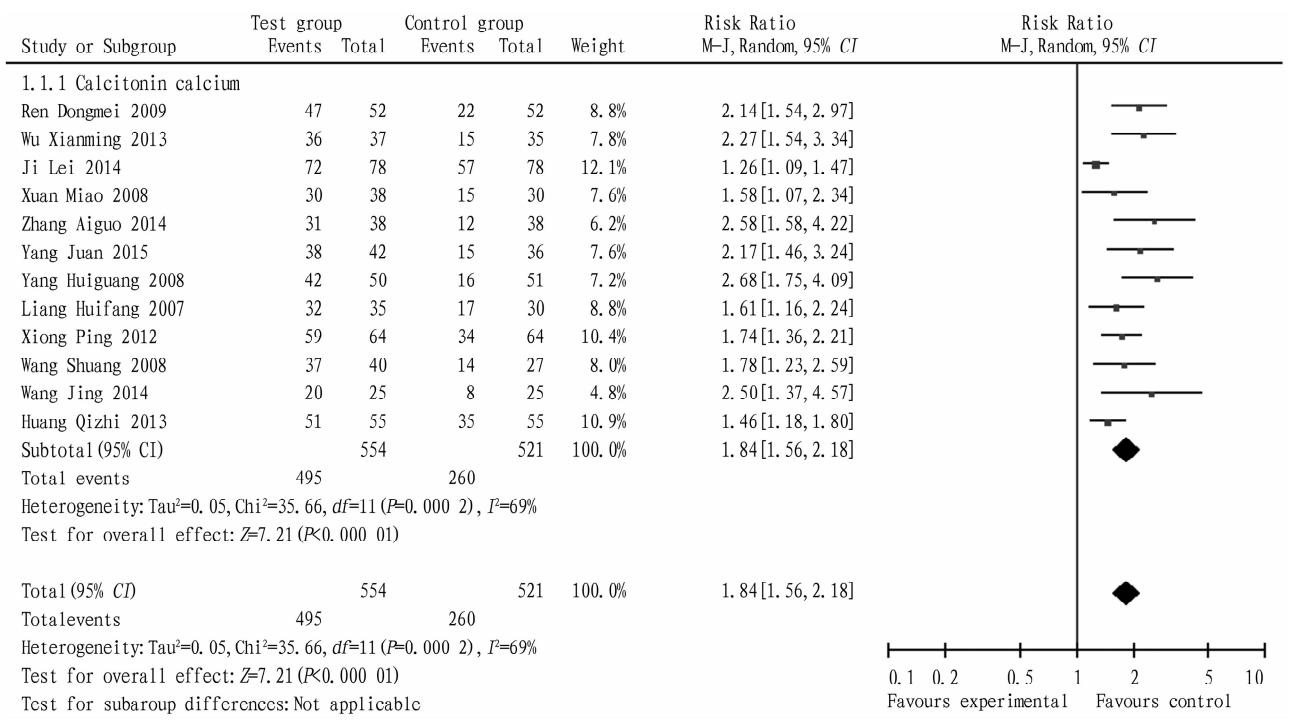

Fig. 1 Meta-analysis forest map of literature study on the effect of salmon calcitonin on bone pain in osteoporosis patients

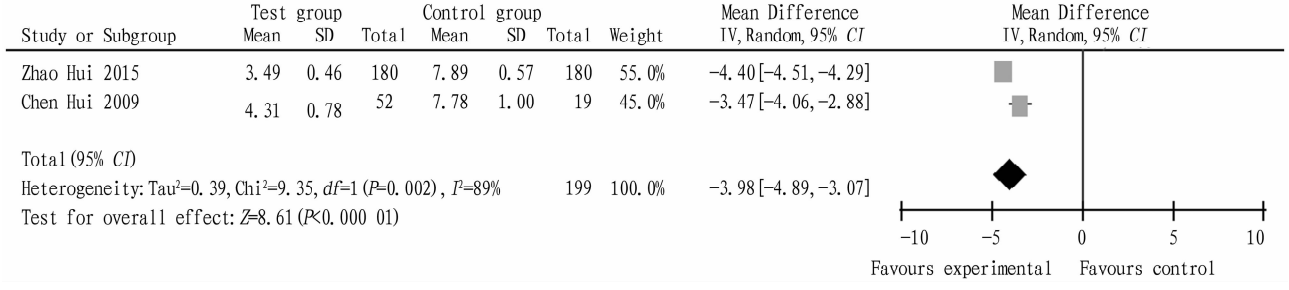

Fig. 2 Meta-analysis forest map of salmon calcitonin on bone pain in osteoporosis patients

of calcitonin combined with calcium. The salmon calcitonin is the most commonly used polypeptide biological preparation for resisting bone mass loss and improving the symptoms of patients with osteoporosis, and has the effects of relieving pain and promoting fracture healing to a certain extent. Lai Xike[16] found that there was no significant difference between imported salmon calcitonin and domestic salmon calcitonin in the curative effect and bone mineral density of postmenopausal osteoporosis patients, and the price of domestic salmon calcitonin was lower.

Following the principles of evidence-based medicine, we used meta-analysis to quantitatively analyze the efficacy and safety of clinical randomized controlled trials of salmon calcitonin in the treatment of osteoporosis collected from January 2000 to March 2022. It improved the power of statistical tests. It is expected to provide more reliable evidence for clinical practice and decision-making than a single study. Besides, meta-analysis was performed based on 13 randomized controlled trials involving 1 683 patients. The results showed that compared with the control group, salmon calcitonin had a good advantage in improving bone pain symptoms in patients with osteoporosis whether it was used alone or in combination, and traditional Chinese medicine had a long history, which had a good application prospect in preventing and treating osteoporosis, improving bone pain symptoms, adjusting patients' physique and improving bone metabolism.

All articles included in this study adopted the principle of random assignment and control, and the results were stable, so the overall credibility of this study was high. However, there are also some problems in the literature, such as the included literature is literature, the sample size is too small, resulting in greater heterogeneity, the lack of blindness may lead to greater bias in the results, no record of the number of people lost to follow-up, and so on. Randomized controlled studies in other languages were not retrieved in this evaluation, and specific osteoporosis types were not subdivided and classified, which may cause distribution bias. These are the shortcomings that need to be overcome in future studies, and better RCT studies will be designed to further verify the above conclusions. In summary, salmon calcitonin can improve the symptoms of bone pain in patients with osteoporosis, and can be used as one of the treatment options for the prevention and treatment of osteoporosis.

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4 Conclusions

Our study developed and validated a rapid, sensitive, and highly specific GC-MS/MS-based MRM method for 1,8-cineole, eugenol, and β-caryophyllene in rat plasma. This method was successfully applied to the pharmacokinetic study of CAVO administered intravenously to rats. The optimized MRM mode demonstrated high sensitivity and stability for the analysis of CAVO, allowing for more accurate quantification of components with high CAVO content. This study is expected to lay a foundation for future methods of CAVO content detection and provides a reference for the analysis of similar Chinese medicine compound volatile oils.

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